Med Sci Monit, 2000; 6(5): 957-963

HLA class I antigens in families with coeliac disease

Anna Kędzierska, Gabriel Turowski

Independent Laboratory of Clinical Immunology, Faculty of Medicine, Collegium Medicum, Jagiellonian University, Cracow, Poland

key words: HLA system, class I antigens, phenotype frequencies, coeliac disease

SUMMARY

The aim of the study was the analysis of the frequency of HLA class I antigens in the Polish population of children suffering from coeliac disease and their families, as well as the estimation of the relative risk of incidence, etiologic fraction (EF) and preventive fraction (PF) indexes. Forty-six probands' families were included in the typing: 69 children with coeliac disease confirmed clinically and histologically, 49 healthy siblings and 91 parents. The HLA antigens were typed with routine Terasaki an McClelland's two-stage microcytotoxic assay in NIH modification. The following antigens occurred significantly more frequently ($p<0.0000...1$) in phenotypes of children with coeliac disease: HLA-A1 ($\chi^2 = 35.90$; RR = 4.3; EF = 0.44), -B8 ($\chi^2 = 88.20$; RR = 8.8; EF = 0.58) and Cw7 ($\chi^2 = 55.24$; RR = 7.5; EF = 0.69). The positive correlation for the specificity of HLA-A1, -B8 was proved also in siblings ($\chi^2 = 16.03$; $\chi^2 = 18.10$) and parents ($\chi^2 = 15.67$; $\chi^2 = 32.67$). The presence of antigens HLA-A1, -B8 in the phenotype may be the risk factor predisposing for the manifestation of hypersensitivity to gluten.

INTRODUCTION

The coeliac disease (CD) is caused by genetically determined pathological immune response to consumed gluten, specifically to gliadin and other prolamines. The introduction of these proteins into diet of a sensitive person results in clinical manifestations of the malabsorption syndrome (primary gluten intolerance) as well as characteristic histological changes of the mucous membrane of small intestine (gluten-sensitive enteropathy) [1,2].

The studies on coeliac disease etiopathogenesis are still being carries out, despite the fact that factor responsible for its clinical manifestations is known. Family studies showed that increased susceptibility to coeliac disease was at least partially genetically determined. The factor responsible for its incidence was mapped on the short arm of 6th chromosome in 6p23 segment [3,4]. Coeliac disease was one of the first disease entities in which positive correlation with some of HLA region antigens was observed. Genetic linkage and coeliac disease associations with HLA system were the subject of investigations in various countries [5–10]. The results of these studies showed primarily the presence of associations with some of the antigens determined by HLA-A and HLA-B loci. At present, a strict correlation between primary gluten intolerance and the presence of the following HLA class II antigens has been proved: HLA-DQ2 (DQA1*0501, DQB1*0201) and HLA-DR3 (DRA, DRB1*0301). The data that confirm the role of genetic factor in etiopathogenesis of coeliac disease therefore attract researchers' attention to genes and the products of the Major Histocompatibility Complex (MHC). Genes HLA-DQA1 and DQB1 encode corresponding subunits of the dimer presenting antigens on the surface of T-lymphocyte immunocompetent cells.

The purpose of the study was the analysis of the frequency of the HLA class I antigens in Polish population of children with coeliac disease con-

Received: 1999.03.08
Accepted: 1999.12.30

Correspondence address: Anna Kędzierska PhD, Independent Laboratory of Clinical Immunology, Faculty of Medicine, Collegium Medicum, Jagiellonian University, ul. Grzegórzecka 16, 31-531 Cracow, Poland

firmed clinically and histologically as well as in their families.

MATERIAL AND METHODS

HLA-ABC antigen typing was conducted in 46 families, including 91 parents and 118 children (49 healthy siblings and 69 children suffering from the disease, treated at the General Paediatric Department of Silesian Medical University in Zabrze and in 2nd Department of Paediatric Diseases of Polish-American Paediatric Institute at the Faculty of Medicine of Jagiellonian University in Cracow. The diagnosis of the proband's disease was based on the criteria established in 1976 in Interlaaken [1,2].

Human histocompatibility antigens of the HLA system determined by HLA-ABC loci were typed with the use of Terasaki and McClelland's routine two-step-microcytotoxic assay [11] in NIH modification [12]. The typing included 14 specificities determined by HLA-A locus, 20 specificities determined by HLA-B locus and biallelic Bw4/Bw6 system, as well as 7 C-locus antigens. At least three different anti-HLA sera were for the typing. They were obtained from the Serum Bank of the National Institute of Health in Bethesda, from the commercial companies, and from the collection of Independent Laboratory of Clinical Immunology of the Faculty of Medicine of Jagiellonian University in Cracow [13].

The control group for the frequency of HLA class I antigens phenotypes was 1152 healthy adults of both sexes living in the regions of Southern Poland [14]. The phenotypes frequencies (f) were calculated with the use of the following equation

f = the number of people with the antigen present in a given phenotype / the number of people examined

The frequency of HLA-ABC antigens in the examined group was compared to the results obtained in control population with the use of chi-squared test. In case of relatively small numbers, i.e. general observation count below 100, Yates' modification was applied. H_0 hypothesis of the absence of significant differences between analysed groups was rejected if the value of chi-squared test exceeded the critical value of $\chi^2_{0.05}$ (for $\alpha = 0.05$) taken from the table worked out by Hawkins [15]. The critical value $\chi^2_{0.05}$ for class I specific antigens for 43 tested equals 10.633.

The power of the association, i.e. the risk to develop the disease in the population with a given HLA antigen in comparison to the group without that antigen was determined by calculating the relative risk value (RR) according to Svejgaard et al. [16]. Etiologic frac-

Table 1. Frequency (f) of HLA-A phenotypes in families of children with coeliac disease, and in the control population.

HLA-A antigens	Children with coeliac disease			Healthy siblings			Parents			Control population	
	N	f	X^2	N	f	X^2	N	f	X^2	N	f
A1	40	57.9710	35.90***	25	51.0204	16.03***	40	43.9560	15.67**	282	24.4792
A2	20	28.9855	8.79*	16	32.6531	3.89	30	32.9670	7.15	554	48.0903
A3	20	28.9855	0.32	10	20.4082	0.34	18	19.7802	1.04	290	25.1736
A9	11	15.9420	2.89	8	16.3265	1.78	18	19.7802	1.34	298	25.8691
A23(9)	2	2.8986	0.60	2	4.0816	0.05	3	3.2967	0.63	68	5.9027
A24(9)	9	13.0435	1.57	6	12.2449	1.32	15	16.4835	0.44	230	19.9653
A10	7	10.1449	3.19	9	18.3673	0.00	14	15.3846	0.72	226	19.6181
A25(10)	5	7.2464	0.41	9	18.3673	2.33	11	12.0879	0.10	120	10.4167
A26(10)	2	2.8986	2.47	-	-	-	3	3.2967	2.97	106	9.2014
A11	5	7.2464	0.92	3	6.1224	0.98	6	6.5934	1.78	136	11.8056
A19	10	14.4928	0.13	12	24.4898	0.70	12	13.1868	1.35	215	18.6632
A29(19)	2	2.8986	0.08	6	12.2449	11.35**	3	3.2967	0.00	31	2.6909
A30(19)	4	5.7971	0.05	2	4.0816	0.06	2	2.1978	0.55	51	4.4271
A31(19)	2	2.8986	0.49	-	-	-	1	1.0989	2.62	65	5.6423
A32(19)	2	2.8986	0.04	3	6.1224	0.44	5	5.4945	0.11	48	4.1667
A33(19)	-	-	-	1	2.0408	0.03	1	1.0989	0.00	20	1.7361
A68(28)	-	-	-	1	2.0408	2.78	3	3.2967	2.69	120	8.8542
Ax	12			10			35			107	

* $p < 0.02 - 0.05$; ** $p < 0.01 - 0.001$; *** $p < 0.0001 - 0.0000...1$

Table 2. Frequency (f) of HLA-B phenotypes in families of children with coeliac disease, and in the control population .

HLA-B antigens	Children with coeliac disease			Healthy siblings			Parents			Control population	
	N	f	X^2	N	f	X^2	N	f	X^2	N	f
B7	16	23.1884	0.49	12	24.4898	0.59	18	19.7802	0.00	219	19.0104
B8	45	65.2174	88.20***	21	42.8571	18.10***	39	42.8571	32.67***	203	17.6215
B13	12	17..3913	4.93	9	18.3673	4.24	13	14.2857	2.56	100	8.6806
B14	-	-	-	3	6.1224	0.02	7	7.6923	1.15	53	4.6007
B15	3	4.3478	0.64	5	10.2041	0.05	7	7.6923	0.00	95	8.2465
B62(15)	3	4.3478	0.64	4	8.1633	0.03	6	6.5934	0.03	89	7.7257
B63(15)	-	-	-	1	2.0408	0.17	1	1.0989	0.00	6	0.5208
B16	2	2.8986	0.98	3	6.1224	0.13	5	5.4945	0.35	100	8.6806
B38(16)	1	1.4493	1.55	2	4.0816	0.03	4	4.3956	0.09	66	5.7292
B39(16)	1	1.4493	0.13	1	2.0408	0.00	1	1.0989	0.49	34	2.9514
B18	1	1.4493	7.67	3	6.1224	1.76	3	3.2967	7.31	159	13.8021
B21	3	4.3478	0.44	-	-	-	3	3.2967	0.38	62	5.3819
B49(21)	1	1.4493	0.32	-	-	-	2	2.1978	0.12	40	3.4722
B50(21)	2	2.8986	0.02	-	-	-	1	1.0989	0.02	22	1.9097
B27	4	5.7971	2.62	1	2.0408	4.35	6	6.5934	2.81	153	13.2813
B35	7	10.1449	2.53	7	14.2857	0.31	16	17.5824	0.01	213	18.4896
B41	1	1.4493	0.01	1	2.0408	0.10	1	1.0989	0.01	7	0.6076
B44(12)	11	15.9420	2.15	10	20.4082	0.23	11	12.0879	6.52	282	24.4792
B51(5)	4	5.7971	1.48	1	2.0408	4.13	9	9.8901	0.05	130	11.2847
B22	2	2.8986	0.12	2	2.0408	0.00	3	3.2967	0.46	64	5.5556
B55(22)	2	2.8986	0.12	2	2.0408	0.00	2	2.1978	0.01	34	2.9514
B56(22)	-	-	-	-	-	-	1	1.0989	0.29	30	2.6042
B57(17)	1	1.4493	1.18	2	4.0816	0.11	2	2.1978	0.98	59	5.1215
B60(40)	1	1.4493	2.83	3	6.1224	0.01	3	3.2967	1.75	88	7.6389
Bx	11			13			30			87	
Bw4	35	50.7246	6.57	30	61.2245	0.39	50	54.9451	4.56	767	66.5799
Bw6	65	94.2029	6.40	45	91.8367	2.77	77	84.6154	0.38	938	81.4236

*** $p < 0.0000...1$

Table 3. Frequency (f) of HLA-C phenotypes in families of children with coeliac disease, and in the control population.

HLA-C antigens	Children with coeliac disease			Healthy siblings			Parents			Control population	
	N	f	X^2	N	f	X^2	N	f	X^2	N	f
Cw1	5	7.2464	0.01	4	8.1633	0.04	14	15.3846	4.21	97	8.4201
Cw2	5	7.2464	2.56	3	6.1224	2.30	15	16.4835	0.05	173	15.0174
Cw3	6	8.6957	3.72	11	22.4490	0.02	14	15.3846	0.40	215	18.6632
Cw4	11	15.9420	2.20	8	16.3265	1.32	20	21.9780	0.18	283	24.5660
Cw5	5	7.2464	0.03	12	24.4898	17.68***	9	9.8901	0.64	81	7.0313
Cw6	12	17.3913	0.00	10	20.4082	0.24	14	15.3846	0.03	192	16.6667
Cw7	55	79.7101	55.24***	32	65.3061	18.15***	51	56.0440	16.12***	397	34.4618
Cwx	18			17			34			106	

*** $p < 0.00001$ - $0.0000...1$

tion index (EF) proposed by Green [17,18] was calculated when RR values were greater than 1. EF index was used to compare the number of people with a given antigen to the frequency of the same antigen in the whole population. EF index provides information about the effect of a given antigen (pathological factor) on the incidence of the disease. In case of negative correlation, the preventive factor index was calculated, in attempt to estimate the proportion of cases with lower risk of disease development due to the absence or low frequency of HLA antigen in phenotype. The values of EF and PF

Table 4. The relative risk (RR), etiologic (EFe, EF) and preventive (PFe,PF) fraction of selected HLA class I antigens in families of children with coeliac disease

HLA antigens	Children with coeliac disease		Healthy siblings		Parents	
			Relative risk RR			
A1	4.2553		3.2137		2.4197	
B8	8.7654		3.5062		3.5062	
Cw7	7.4712		3.5798		2.4247	
A29(19)	1.0794		5.0458		1.2328	
B13	2.2147		2.3670		1.7533	
Cw5	1.0330		4.2883		1.4512	
B18	0.1864		0.4073		0.2129	
B27	0.4018		0.1360		0.4609	
B44(12)	0.6495		0.7911		0.4242	
			Etiologic fraction			
	EFe	EF	EFe	EF	EFe	EF
A1	0.7650	0.4435	0.6888	0.3514	0.5867	0.2579
B8	0.8859	0.5778	0.7148	0.3064	0.7148	0.3064
Cw7	0.8662	0.6904	0.7207	0.4707	0.5876	0.3293
A29(19)	1.0794	0.0736	0.8018	0.0981	0.1888	0.0062
B13	0.5485	0.0954	0.5775	0.1061	0.4296	0.0614
Cw5	0.0319	0.0019	0.7668	0.1878	0.3109	0.0307
			Preventive fraction			
	PF_E	PF	PF_E	PF	PF_E	PF
A2	0.5278	0.2538	0.4766	0.2292	0.4691	0.2797
A23(9)	0.5241	0.0310	0.3217	0.0189	0.8142	0.0462
A26(10)	0.7054	0.0651	-	-	0.6636	0.0611
B18	0.8136	0.1124	0.5927	0.0818	0.7871	0.1088
B27	0.5982	0.0795	0.8640	0.1146	0.5391	0.0391
B44(12)	0.3505	0.0859	0.2089	0.0511	0.5758	0.1409
B38(16)	0.7580	0.0435	0.2998	0.0171	0.2435	0.0139
B57(17)	0.7276	0.0375	0.2117	0.0108	0.5837	0.0298
B60(40)	0.8222	0.0627	0.2115	0.0161	0.5878	0.0449

indexes may range from 0 (no correlation) to 1.0 (maximum correlation).

When positive correlation was observed, i.e. there was a statistically significant correlation, the etiologic fraction coefficient (EF_e) proposed by Green was calculated for the exposed people. In this way, the proportion of cases with developed disease among the population at risk could be estimated. In the case of negative correlation, the preventive factor coefficient (PF_E) was calculated as the proportion of cases protected in the exposure to people from the whole population at risk of developing the disease.

RESULTS

The frequencies of HLA-ABC phenotypes in the population of affected children, healthy siblings and parents are presented in tables 1, 2, 3 along with the results of the frequencies for the population of 1152 healthy controls [14]. The analysis of the frequencies of the antigens determined by locus A indicates that the frequency of HLA-A1 antigen in the group of probands ($\chi^2 = 35.90$, $p<0.000...1$) is significantly higher, while the frequency of HLA-A2 phenotypes is significantly lower than in the control group ($\chi^2 = 8.79$; $p<0.025$).

The frequencies of HLA-A antigens also indicate that there is a correlation (with high statistical significance of the differences) between HLA-A1 in parents ($\chi^2 = 15.67$, $p<0.001$) and healthy siblings ($\chi^2 = 16.03$, $p<0.0000...1$) and, additionally, the HLA-A29 antigen in healthy children ($\chi^2 = 11.35$, $p<0.01$) (table 1). Moreover, lower frequency of HLA-A2 antigen was observed, with χ^2 values equalling 7.15 and 3.89, respectively, and it proved statistically insignificant according to Hawkins' table [15]. The frequency of the remaining antigens determined by locus A was comparable with control population in all examined groups.

Among the antigens determined by locus B, highly significant differences were observed for the HLA-B8 antigen ($\chi^2 = 88.20$, $p<0.0000...1$) in children with coeliac disease when compared to the results obtained in control subjects. Positive correlation for this specificity was also observed in healthy siblings ($\chi^2 = 18.10$, $p<0.005$) and parents ($\chi^2 = 32.67$; $p<0.0000...1$). It was also found that in probands' families, HLA-B13 antigen occurred more frequently ($\chi^2 = 2.56–4.93$) when compared to control group, but without statistical significance. On the other hand, HLA-B18, -B27 and –B44(12) antigens tended to occur less frequently in phenotypes in all the analysed family members than in healthy population (table 2).

Among locus C antigens, highly significant differences ($p<0.0000...1$) in comparison to the control group were found for the HLA-Cw7 specificity. The differences were observed with respect to children with coeliac disease, siblings and parents. Chi^2 test value for them equalled 55.24, 18.15 and 17.04, respectively. In the group of children with no manifestation of the pathological process, significantly higher frequency of HLA-Cw5 antigen was also shown with χ^2 value = 17.68, $p<0.00025$ (table 3).

In the analysis of the relative risk of developing the disease calculated for the antigens determined by

A, B and C loci, specificities HLA-A1, -B8 and Cw7 present in haplotype are deserve special attention (table 4). The highest RR values were observed mainly in the population of children with coeliac disease and equalling 4.2553, 8.7654 and 7.4712, for respective antigens. RR values related to the frequency of these antigens in healthy siblings and parents were lower, equalling 3.2137 and 2.4197 for HLA-A1, respectively. The values of relative risk for the rest of the antigens determined by ABC loci were lower than 1, except HLA-B13 and HLA-Cw5 specificities.

The analysis of etiologic fraction of HLA-ABC antigens shows that calculated EF values corresponded to the values of the relative risk (RR) of the disease.

When HLA-A1 antigen was inherited in the population of affected children, the values of EF_e and EF were 0.7650 and 0.4435, respectively, and in the case of inheriting HLA-B8, they were 0.8859 and 0.5778. The inclination for developing the disease was estimated at 44.35% and 57.78%.

Similar comparison was drawn for the population of mothers and fathers as well as healthy siblings. Its outcomes are presented in table 4. The analysis of EF_e and EF shows that in case of HLA-A1, -B8, -Cw7 antigen EF values in parents and siblings were lower than those in affected children. Parental EF of HLA-A1 antigen equalled 0.2579, while it was 0.3514 in healthy siblings. In affected children, EF for the A1 antigen equalled 0.4435. Although in the case of HLA-B8 specificity high values of EF_e and EF indexes were calculated (EF_e = 0.8859, EF=0.5778) for the group of children with the manifestations of the disease, these values were only slightly lower in their parents and siblings, amounting to EF_e = 0.7148, EF=0.3064, respectively, in both analysed groups.

PF_E values were high for HLA-A2, -B18, -B27, -B44(12) antigens, ranging between 0.3505 and 0.8136 in affected children with low PF value oscillating between 0.0795 and 0.2538. Similar PF_E values were calculated for healthy siblings (0.2089-0.8640) and parents (0.4691-0.7871) with equally low preventive factor index value. High PF_E values were also calculated for HLA-A23(9), -A26(10), -B38(16), -B57(17) and -B60(40) antigens. It referred mainly to the population of affected children and their parents. This may indicate the proportion of cases with this particular antigen, protected in exposure to incidence factors in relation to the whole hypothetical number of people who might develop the disease.

DISCUSSION

The studies on the frequency of HLA antigens in families of children suffering from coeliac disease allowed to estimate the frequency of phenotypes for specific HLA class I antigens. Statistical analysis showed significantly higher frequency of HLA-A1, -B8 ($p<0.00001$–$0.0000...1$) together with linked -Cw7 antigen. The highest frequency was obtained in affected children. Similar correlation (although to lower extent) was discovered in parents and healthy siblings. Additionally, significantly higher frequencies of HLA-A29(19) and HLA-Cw5 phenotypes were observed in affected children when compared to control population.

Up to now, the calculation of the relative risk of the disease (RR) was used as a rule, in order to estimate the differences between HLA phenotypic expression in the population of healthy and affected people. If the differences in the frequency of a given HLA specificity were statistically significant and RR values were high, it indicated a correlation between HLA class I and class II antigens characteristic for specific disease entity.

Svejgaard et al. [16] and Green [17,18] made an attempt to express the relationship between the risk of incidence and the index of 'incidence condensation', etiologic fraction index and preventive fraction index in mathematical terms. This is of particular importance in causative-heterogeneous diseases. According to the authors, one can assume that the effect of the dose of the gene determining disease incidence is included in the value of calculated fraction. The estimated RR values related to A1 and B8 antigens proved low. They were approximately twice as large in children with coeliac disease as in the analysed group of parents and healthy siblings. The highest relative risk of developing coeliac disease related to B8 antigen might have been secondarily determined by HLA-B8 and HLA-DR3 and DR7 linkage disequilibrium effect [5,19,20].

Winklhofer-Roob et al. [20] presented an overview of the frequency of antigens related to coeliac disease (i.e. HLA-B8, -DR3, -DR7) in 9 different populations, without presenting HLA-B8 frequency in three of them. This specificity was 2-3 times more frequent in all the examined populations in comparison to control population. The frequency of HLA-DR3 antigen was 2-4 times higher.

The frequency of HLA antigens phenotypes in various groups of family members was not a subject of comprehensive analysis by Polish authors, except for Siekiera's studies published in 1992 [21]. The author confirmed significantly more frequent occurrence of HLA-A1, -B8, -DR3 antigens in phenotypes of patients with gluten malabsorption syndrome, analysing the determinations of the antigens of HLA-ABC, DR system and other genetic markers in 51 probands' families. She pointed to a correlation present with these antigens by the analysis of antigens determined by A and B loci in parents and healthy siblings. Lower frequency of HLA-B17 antigen (χ^2 = 4.720) in parents and twice more frequent HLA-B44(12) antigen (χ^2 = 3.514) observed by Siekiera were not confirmed in this study. The frequencies of phenotypes of the remaining HLA-ABC antigens in relation to healthy population did not differ both in Siekiera's studies and in our analysis [22]. The only exceptions were HLA-A29(19) and HLA-Cw5 antigens, observed significantly more frequently in healthy siblings.

The comparison of the relative risk of disease incidence calculated by Siekiera [21] and the one presented in this study shows that RR values for HLA-A1 were similar and equalled 3.9565 and 4.2553, respectively. On the other hand, the values for HLA-B8 antigen were different and equalled 5.6040 and 8.7657. Johannsen [23] presented the results quoted by eleven different authors, who estimated the relative risk of developing coeliac disease related to HLA-B8 antigen at 8.63 and it was similar to the value estimated in this study.

The analysis of HLA-A and HLA-B frequencies carried out by Łukasik et al. [24] in the group of 107 children suffering from coeliac disease showed that HLA-A1 and Ax antigens were more frequent in affected children than in control population of healthy people, while HLA-A3 and A-19 antigens occurred less frequently. The relative risk equalled 3.5; 1.26; 0.41 and 0.45, respectively. Having performed a statistical analysis, the authors did not find any basis on which the hypothesis that the difference in frequencies of A1, A3 and Ax antigens was statistically significant could have been rejected. For the remaining locus A antigens including wide specificity of HLA-A19, the difference proved insignificant. Although Hetzel et al. [25] found positive a correlation between coeliac disease and HLA-A23(9) antigen, the frequency of this specificity in examined group and their families was similar to control population. De Marchi et al. [19] list HLA-A30 and HLA-B13 among the antigens related to coeliac disease as the ones with marked tendency for increased frequency.

The distribution of HLA class I antigens frequency in children suffering from coeliac disease and their families seems to differ greatly. The association of the positive associations between coeliac disease and HLA class I antigens is still valid, because the determination of their soluble form (sHLA) proved significant [22]. Presently, it is a fact, that DQ2 particle plays a significant role in the pathogenesis of coeliac disease as the restriction component for gliadin-specific T lymphocytes in the alimentary tract [26,27]. However, the question why and how coeliac disease develops only in 20% of general population of predisposed individuals with 'risk alleles' encoding DQ2 particles in their genome still remains unanswered.

CONCLUSIONS

1. The presence of HLA-A1, -B8 antigens in phenotype may be a risk factor predisposing for the manifestation of hypersensitivity to gluten.

2. The determination of these antigens can be helpful for the problem of familial incidence of the disease with different expression and clinical course.

REFERENCES:

1. *Mäki M, Collin P: Coeliac disease. Lancet, 1997; 349: 1755-1759*
2. *Epidemiologia, diagnostyka i leczenie celiakii. Med Prakt, Wyd specjalne, 1998; 2: 1-31*
3. *Michalski JP, McCombs CC: Celiac disease: clinical features and pathogenesis. Am J Med Sci, 1994; 3: 204-211*
4. *Houlston RS, Tomlinson IP, Ford D et al: Linkage analysis of candidate regions for coeliac disease genes. Hum Mol Genet, 1997; 6: 1335-1339*
5. *Thorsby E, Lundin KE, Rønningen KS et al: Molecular basis and functional importance of some disease - associated HLA polymorphism. Tissue Antigens, 1989; 34: 39-49*
6. *Greenberg DA, Hodge SE, Rotter JI: Evidence for recessive and against dominant inheritance at the HLA - "linked" locus in coeliac disease. Am J Hum Genet, 1982; 34: 263-277*
7. *Falchuk ZM, Rogentine GN, Strober W: Predominance of histocompatibility antigen HLA8 in patients with gluten-sensitive enteropathy. J Clin Invest, 1972; 51: 1602-1605*
8. *Ludwig H, Polymenidis Z, Granditsch G, Wick G: HL-A1 und HL-A8 bei kindlicher Coeliakie. Z Immun Forsch Bd, 1973; 146: 158-167*
9. *McNeish AS, Nelson R, Mackintosh P: HL-A1 und 8 in childhood coeliac disease. Lancet, 1973; 1: 668-673*
10. *Tighe MR, Ciclitira PJ: The implications of recent advances in coeliac disease. Acta Paediatr, 1993; 82: 805-810*

11. *Terasaki PI, McClelland JD: Microdroplet assay of human serum cytotoxins. Nature (London), 1964; 204: 998-999*
12. *NIH lymphocytes microcytotoxicity technique [in:] NIAID Manual of Tissue Typing Techniques, 1976-1977; NIH DHEW Publ Sept 22-23: 1976*
13. *Kędzierska A, Gieracka D, Turowski G: Selekcja poliklonalnych limfocytotoksycznych surowic anty HLA-ABC. Arch Med Sąd Krym, 1993; 43: 136-142*
14. *Turowski G: Układ zgodności tkankowej człowieka HLA. I. Częstości fenotypowe i genowe antygenów HLA-ABC w polskiej populacji. Arch Med Sąd Krym, 1992; 42: 221-224*
15. *Hawkins BR: Table of critical chi-square value for investigation involving multiple comparisions. Tissue Antigens, 1981; 17: 243-244*
16. *Svejgaard A, Platz P, Ryder LL: HLA and disease susceptibility: clinical implications. Clin Immunol Allergy, 1984; 4: 567-573*
17. *Green A: Epidemiologic considerations on studies of HLA and disease associations. I. The basic measures, concepts and estimation procedures. Tissue Antigens, 1982; 19: 245-258*
18. *Green A: The epidemiologic approach to studies of associations between HLA and disease: II. Estimation of absolute risks, etiologic and preventive fraction. Tissue Antigens, 1982; 19: 259-268*
19. *De Marchi M, Carbonara A, Ansaldi N et al: HLA-DR3 and DR7 in coeliac disease: immunogenetic and clinical aspect. Gut, 1983; 24: 706-712*
20. *Winklhofer-Roob BM, Rossipal E, Lanzer G: Human leucocyte class I and II antigens in coeliac disease: a study in Austrian paediatric population. Eur J Pediatr, 1991; 150: 704-707*
21. *Siekiera U: Antygeny układu HLA-ABC. DR i inne wybrane markery genetyczne u dzieci chorych z celiakią. Rozprawa doktorska, Wydz Farmaceutyczny Śląskiej Akademii Medycznej, Katowice-Kraków, 1992*
22. *Kędzierska A: Immunogenetyczne aspekty choroby trzewnej u dzieci. Rozprawa doktorska, Wydz Lekarski Collegium Medicum Uniwersytetu Jagiellońskiego, Kraków, 1998*
23. *Johannsen R: HLA and disease association. Behring Institute, Hoechst, Frankfurt/M, 1980*
24. *Łukasik M, Kasner J, Siekiera U et al: Częstość występowania antygenów HLA-A, HLA-B i HLA-DR u chorych z celiakią. Immunol Pol, 1990; 15: 343-352*
25. *Hetzel PA, Bennett GD, Sheldon AB et al: Genetic markers in Australian Caucasian subjects with coeliac disease. Tissue Antigens, 1987; 30: 18-22*
26. *van de Wal Y, Kooy YM, Drijfhout JW et al: Peptide binding characteristics of the coeliac disease-associated DQ (α1*0501, β1*0201) molecule. Immunogenetics, 1996; 44: 246-253*
27. *Molberg O, Kett K, Scott H et al: Gliadin specific, HLA-DQ2-restricted T cells are commonly found in small intestinal biopsies from coeliac disease patients, but not from controls. Scand J Immunol, 1997; 46: 103-109*